Chem Biol Drug Des 2010; **76:** 130–141

Research Article

doi: 10.1111/j.1747-0285.2010.00990.x

1,4-Thienodiazepine-2,5-diones via MCR (II): Scaffold Hopping by Gewald and Ugi-Deprotection-Cyclization Strategy

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A second scaffold of 1,4-thienodiazepine-2,5-diones was discovered and is synthetically accessible from Gewald 2-aminothiophenes via Ugi-Deprotection-Cyclization (UDC) strategy. This approach yielded hybrid peptidomimetic diazepine structures with six points of diversity introduced from readily available starting materials. A virtual compound library (*N* = 50 000) was generated and evaluated for chemical space distribution and drug-like properties.

Key words: 1,4-thienodiazepine-2,5-dione, 2-aminothiophene, Gewald reaction, multicomponent reaction, peptidomimetic, Ugi reaction

Abbreviations: BDZ, 1,4-benzodiazepine-2,5-dione; G-3CR, Gewald three-component reaction; MCR, multicomponent reaction; TBD, 1,5,7-triazabicyclo[4,4,0]dec-5-ene; TDZ, 1,4-thienodiazepine-2,5-dione; UDC, Ugi-Deprotection-Cyclization; U-4CR, Ugi four-component reaction.

Received 21 January 2010, revised 14 April 2010 and accepted for publication 18 April 2010

The synthesis and evaluation of new scaffolds based on privileged structures play an important role in the drug discovery process. Privileged structures are often preferentially chosen by medicinal chemists, as there is the belief that the 'spirit' of an approved and successful compound based on such a scaffold can be transferred into a new compound for a different indication (1). Over 40 medications highlight 1,4-benzodiazepine as a classic privileged structure with a broad range of therapeutic treatment (2). As the discovery of benzodiazepine family, many synthetic derivatives with a wide pharmacological spectrum have been extensively developed (3,4). For example, farnesyltransferase (FTase) inhibitor BMS-214662 has undergone evaluation as an anti-cancer drug in phase I and II clinical trials (5). Moreover, 1,4-benzodiazepines may act as mimetics of peptide secondary structures such as α-helix and β-turn, because of their unique structural motifs and physicochemical properties (6–9). It is noteworthy that 1,4-benzodiazepine-2,5-diones (BDZ) as a subfamily of benzodiazepine scaffolds have been synthesized as cyclic peptide structures with diversely substituted moieties (10–12). Recently, hybrid peptidomimetic BDZs have been investigated during the lead generation process, such as tripeptide compounds **1-3** (Figure 1) (13–17). Therefore, the development of new synthetic scaffolds based on 1,4-diazepines has attracted considerable attention in the design of biologically active compounds (18,19).

The chemistry developed based on 1,4-benzodiazepine scaffolds has contributed to the emergence of thiophene as a useful isostere of a benzene ring (20). Bioisosterism successfully led to the discovery of a series of 1,4-thienodiazepine drugs (such as olanzapine, clotiazepam, and brotizolam), which are heterocyclic compounds containing a 1,4-diazepine ring fused to a thiophene ring. It is of great interest to develop the synthesis of new 1,4-thienodiazepine scaffolds, which are much less investigated compared to 1,4-benzodiazepines. Recently, compound **4** has been identified as an inhibitor of MAPKAP kinase-2 (MK-2) (21). The cocrystal structure of compound **4** and MK-2 complex reveals the unique properties of a 1,4-thienodiazepine scaffold (Figure 2) (21). However, chemical space and the structural biology of 1,4-thienodiazepines are still largely unexplored. We are particularly interested in the synthesis of new 1,4-thienodiazepine-2,5-dione (TDZ) scaffolds, which have been not investigated as potential pharmacophore so far.

Multicomponent reaction (MCR) chemistry is particularly useful for the fast and efficient discovery of diverse scaffolds (22). Isocyanide-based MCRs provide powerful tools for producing diverse arrays of compounds with high atom economy (23). In search of a novel synthetic route for the construction of TDZ scaffolds, 2-aminothiophene has been considered as the most appropriate precursor. Gewald three-component reaction (G-3CR) is a unique method using elemental sulfur to yield 2-aminothiophenes **5**, which builds a platform for the synthesis of new thiophene scaffolds (24,25). We found that Gewald 2-aminothiophene is clearly an isostere of anthranilic acids (26). Ugi four-component reaction (U-4CR) is known to be one of the most versatile tools for the construction of α-aminoacylcarbonamides and related backbones (27). For example, orthogonally protected anthranilic acids were used as a key synthon for the synthesis of 1,4-benzodiazepin-2,5-diones via the Ugi-Deprotection-Cyclization (UDC) approach (28–31). In our recent study, we developed UDC strategy using 2-aminothiophene derivatives **6** and ethyl glyoxalate to access TDZ derivatives as potential p53-Mdm2 antagonists (32). Herein, we utilized the UDC strategy (Figure 3) to synthesize another new scaffold of TDZs starting from 2-aminothiophenes, which were prepared by Gewald reactions.

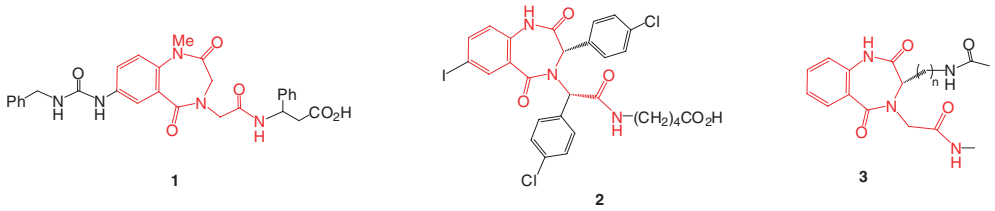


Figure 1: Hybrid peptidomimetic 1,4-benzodiazepine-2,5-diones.

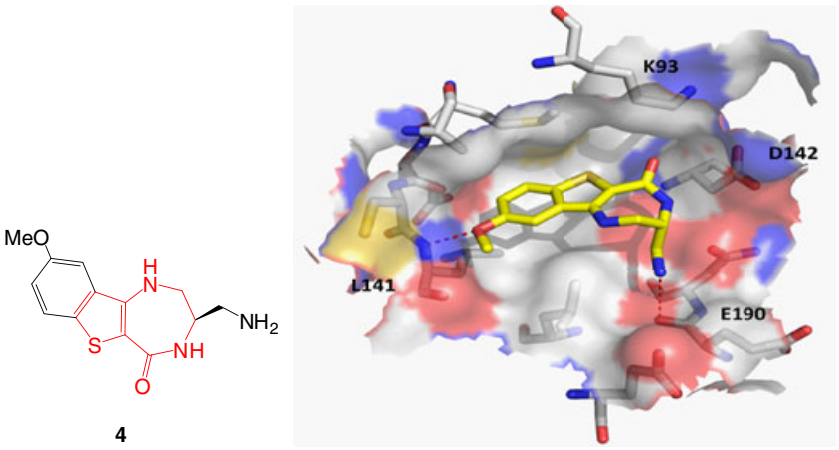


Figure 2: X-ray crystal structure of compound **4** bound to MAPKAP kinase-2 (MK-2, PDB code: 3FYK). Compound **4** is shown in sticks. The receptor binding pocket is shown, and some amino acids are labeled. The hydrogen-bonding network is shown in dash lines.

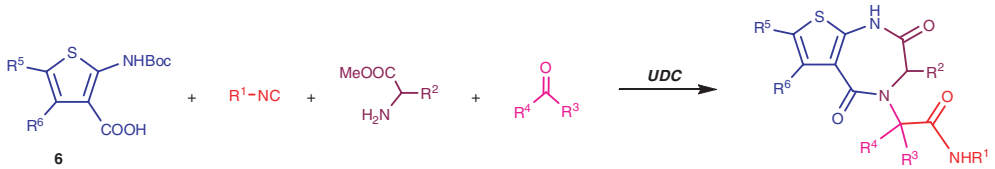


Figure 3: Ugi-Deprotection-Cyclization approach for the synthesis of 1,4-thienodiazepine-2,5-dione scaffolds (R^1, R^2, R^3, R^4, R^5, R^6: points of diversity).

Materials and Methods

General

All reagents were purchased from commercial sources and used without further purification. The reactions were conducted under air atmosphere unless otherwise indicated. Analytical thin-layer chromatography (TLC) was performed on SiO_2 plates on Alumina available from Whatman. Visualization was accomplished by UV irradiation at 254 nm. Chromatography was conducted using Preparative Silica gel TLC plates (1000 μm, 20 cm×20 cm). Proton and carbon NMR spectra were determined on Bruker Avance™ 600 MHz NMR spectrometer. Chemical shifts are reported as δ values in parts per million (ppm) as referenced to residual solvent. ^{1}H NMR spectra are tabulated as follows: chemical shift, number of protons, multiplicity (s = singlet, br.s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant. High-resolution mass spectra were obtained at the University of Pittsburgh Mass Spectrometry facility. LC-MS analysis was performed on an SHIMADZU instrument, using an analytical C18 column (Dionex Acclaim 120 Å, 2.1 × 50 mm, 3.0 μm, 0.2 mL/min). Acetonitrile/water mixtures were used as mobile phase for reverse-phase HPLC coupled to electrospray ionization-mass spectrometry.

***N*-(*tert*-butyl)-2-(2,5-dioxo-1,2,3,5,6,7,8,9-octahydro-4H-[1]benzothieno[2,3-e][1,4] diazepin-4-yl)acetamide (7a, Method A):** The mixture of **6a** (59.4 mg, 0.2 mmol), glycine methyl ester hydrochloride (0.2 mmol, 25.0 mg), triethylamine (0.2 mmol, 27.9 μL), aqueous formaldehyde (0.2 mmol, 14.9 μL), *tert*-butyl isocyanide (0.2 mmol, 22.6 μL) in 0.5 mL of methanol was stirred under RT for 2 days. The reaction was quenched by water and extracted with dichloromethane. The organic layer was washed with saturated potassium carbonate (aq) and dried over anhydrous sodium sulfate. After the evaporation of the solvent, the residue was treated with 0.5 mL of TFA, and stirred under RT for 24 h. To

the reaction was added 10 mL of DCM, then neutralized by saturated potassium carbonate (aq). The mixture was extracted with DCM, the organic layer was combined and dried over anhydrous sodium sulfate. After the evaporation of the solvent, the residue was treated with triethylamine (50 μL) and 1,5,7-triazabicyclo[4,4,0]-dec-5-ene (TBD) (10 mg) in 0.5 mL of THF, and stirred overnight under 40 °C. **7a** was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 2:1) as yellowish solids (32 mg, yield: 46% over three steps). HPLC/MS: t_R = 9.42 min; m/z = 350.1 $[M+H]^+$ HRMS: 349.145979 (found); $C_{17}H_{23}N_3O_3S$, 349.14601 (calcd.). ^{1}H NMR (600 MHz, $CDCl_3$): 1.33 (9H, s), 1.77 (2H, m), 1.83 (2H, m), 2.62 (2H, m), 2.76 (2H, m), 4.08 (2H, s), 4.12 (2H, s), 6.21 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$): 22.3, 23.0, 24.5, 25.8, 28.7, 51.5, 52.5, 52.7, 121.7, 129.2, 135.0, 141.4, 164.4, 167.4, 169.0.

***N*-(cyclopropylmethyl)-2-(2,5-dioxo-1,2,3,5,6,7,8,9-octahydro-4H-[1]benzothieno [2,3-e][1,4]diazepin-4-yl)acetamide (7b, Method A):** The product was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 2:1) as yellowish solids (12 mg, yield: 17% over three steps). HPLC/MS: t_R = 9.12 min; m/z = 348.1 $[M+H]^+$ HRMS: 347.131963 (found); $C_{17}H_{21}N_3O_3S$, 347.13036 (calcd.). ^{1}H NMR (600 MHz, $CDCl_3$): 0.19 (2H, m), 0.48–0.50 (2H, m), 0.94 (1H, m), 1.77–1.84 (4H, m), 2.64 (2H, m), 2.77 (2H, m), 3.11 (2H, m), 4.10 (2H, s), 4.21 (2H, s), 6.49 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$): 3.4, 10.5, 22.3, 23.0, 24.5, 25.8, 44.3, 52.0, 52.5, 121.7, 129.2, 135.1, 141.3, 164.5, 168.0, 168.8.

***N*-(2-phenylethyl)-2-(2,5-dioxo-1,2,3,5,6,7,8,9-octahydro-4H-[1]benzothieno[2,3-e] [1,4]diazepin-4-yl)acetamide (7c, Method A):** The product was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 2:1) as yellowish solids (10 mg, yield: 13% over three steps). HPLC/MS: t_R = 9.81 min; m/z = 398.1 $[M+H]^+$ HRMS: 397.145798 (found); $C_{21}H_{23}N_3O_3S$, 397.14601 (calcd.). ^{1}H NMR (600 MHz, $CDCl_3$): 1.77–1.83 (4H, m), 2.63 (2H, m), 2.73 (2H, m), 2.80 (2H, m), 3.51 (2H, m), 3.99 (1H, s), 4.15 (2H, s), 6.48 (1H, m), 7.17–7.21 (3H, m), 7.25–7.28 (2H, m). ^{13}C NMR (150 MHz, $CDCl_3$): 22.3, 23.0, 24.5, 25.8, 35.5, 40.6, 52.1, 52.4, 121.5, 126.5, 128.6, 128.8, 129.1, 135.0, 138.7, 141.6, 164.5, 168.2, 168.7.

***N*-(*tert*-butyl)-2-(2,5-dioxo-1,2,3,5,6,7,8,9-octahydro-4H-[1]benzothieno[2,3-e][1,4] diazepin-4-yl)-3-methylbutanamide (7d, Method A):** The product was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 2:1) as yellowish solids (12 mg, yield: 15% over three steps). HPLC/MS: t_R = 10.69 min; m/z = 392.2 $[M+H]^+$ HRMS: 391.192703 (found); $C_{20}H_{29}N_3O_3S$, 391.19296 (calcd.). ^{1}H NMR (600 MHz, d^6-DMSO): 0.72 (3H, d, J = 6.0 Hz), 0.89 (3H, d, J = 6.6 Hz), 1.23 (9H, s), 1.61–1.78 (5H, m), 2.10 (1H, m), 2.58 (2H, m), 3.16 (1H, m), 3.86 (1H, d, J = 14.4 Hz), 4.63 (1H, d, J = 10.8 Hz), 7.72 (1H, s). ^{13}C NMR (150 MHz, d^6-DMSO): 19.2, 19.6, 22.5, 23.1, 24.4, 26.1, 28.0, 28.8, 47.2, 50.7, 50.8, 121.0, 127.2, 134.5, 159.9, 164.2, 169.9.

***N*-(*tert*-butyl)-1-(2,5-dioxo-1,2,3,5,6,7,8,9-octahydro-4H-[1]benzothieno[2,3-e][1,4] diazepin-4-yl)cyclohexanecarboxamide (7e, Method A):** The product was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 2:1) as yellowish solids (8 mg, yield: 10% over three steps). HPLC/MS: t_R = 11.00 min; m/z = 418.3 $[M+H]^+$ HRMS: 440.1981 (found); $C_{22}H_{31}N_3NaO_3S$, 440.19783 (calcd.). ^{1}H NMR (600 MHz, CD_3OD): 1.34 (9H, s), 1.45–1.51 (3H, m), 1.61–1.65 (2H, m), 1.81–1.92 (6H, m), 2.03 (2H, m), 2.23 (1H, m), 2.45 (1H, m), 2.67 (2H, m), 2.97 (1H, m), 4.11 (2H, s), 6.55 (1H, s). ^{13}C NMR (150 MHz, CD_3OD): 22.2, 22.8, 23.9, 25.1, 25.7, 27.48, 27.50, 46.8, 50.7, 50.8, 66.69, 66.71, 122.6, 128.4, 134.4, 142.1, 165.4, 170.7, 174.3.

***N*-(*tert*-butyl)-2-(4-chlorophenyl)-2-(2,5-dioxo-1,2,3,5,6,7,8,9-octahydro-4H-[1] benzothieno[2,3-e][1,4]diazepin-4-yl)acetamide (7f, Method B):** The mixture of **6a** (59.4 mg, 0.2 mmol), glycine methyl ester hydrochloride (0.2 mmol, 25.0 mg), triethylamine (0.2 mmol, 27.9 μL), *o*-chloro-benzylaldehyde (0.2 mmol, 28.0 mg), *tert*-butyl isocyanide (0.2 mmol, 22.6 μL) in 0.5 mL of methanol was stirred under RT for 2 days. The reaction was quenched by water and extracted with DCM. The organic layer was washed with saturated potassium carbonate (aq) and dried over anhydrous sodium sulfate. After the evaporation of the solvent, the residue was treated with 0.5 mL of TFA, and stirred under RT for 24 h. To the reaction was added 10 mL of DCM, then neutralized by saturated potassium carbonate (aq). The mixture was extracted with DCM, the organic layer was combined and dried over anhydrous sodium sulfate. After the evaporation of the solvent, **7f** was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 2:1) as yellowish solids (34 mg, yield: 37% over two steps). HPLC/MS: t_R = 11.08 min; m/z = 460.1 $[M+H]^+$ HRMS: 459.137649 (found); $C_{23}H_{26}ClN_3O_3S$, 459.13834 (calcd.). ^{1}H NMR (600 MHz, CD_3OD): 1.31–1.34 (2H, m), 1.38 (9H, s), 1.74–1.90 (4H, m), 2.67 (2H, m), 3.23 (1H, m), 3.87 (1H, m), 6.22 (1H, s), 7.33 (2H, d, J = 7.8 Hz), 7.43 (2H, d, J = 7.8 Hz), 7.94 (1H, s). ^{13}C NMR (150 MHz, CD_3OD): 7.8, 22.2, 22.8, 23.9, 25.5, 27.4, 46.5, 51.2, 120.7, 128.2, 128.8, 130.8, 134.1, 134.2, 134.4, 142.8, 165.1, 169.3, 169.6.

***N*-(*tert*-butyl)-2-(2,5-dioxo-1,2,3,5,6,7,8,9-octahydro-4H-[1]benzothieno[2,3-e][1,4] diazepin-4-yl)-3-phenylpropanamide (7g, Method B):** The product was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 2:1) as yellowish solids (18 mg, yield: 21% over two steps). HPLC/MS: t_R = 11.03 min; m/z = 440.3 $[M+H]^+$ HRMS: 439.193597 (found); $C_{24}H_{29}N_3O_3S$, 439.19296 (calcd.). ^{1}H NMR (600 MHz, d^6-DMSO): 0.86 (1H, s), 1.22 (9H, s), 1.61–1.69 (4H, m), 2.55 (2H, s), 2.88 (1H, m), 3.14 (1H, m), 3.96 (1H, m), 5.36 (1H, s), 7.22 (1H, m), 7.26 (3H, m), 7.29 (1H, m), 7.44 (1H, m), 7.51 (1H, s). ^{13}C NMR (150 MHz, d^6-DMSO): 22.4, 23.1, 24.3, 26.0, 28.2, 28.8, 35.8, 48.0, 50.9, 57.6, 120.7, 126.6, 127.1, 128.4, 129.4, 134.6, 137.9, 164.0, 169.7.

Methyl 2-(2-(*tert*-butoxycarbonylamino)-*N*-(2-(*tert*-butylamino)-2-oxoethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamido)-3-methylbutanoate (8): The mixture of **6a** (74.3 mg, 0.25 mmol), valine methyl ester hydrochloride (0.25 mmol, 41.8 mg), triethylamine (0.25 mmol, 34.8 μL), aqueous formaldehyde (0.25 mmol, 18.6 μL), *tert*-butyl isocyanide (0.25 mmol, 28.3 μL) in 0.5 mL of methanol was stirred under RT for 1 day. The reaction was quenched by water and extracted with DCM. The organic layer was washed with saturated potassium carbonate (aq) and dried over anhydrous sodium sulfate. After the evaporation of the solvent, the product was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 3:1) as yellowish solids (90 mg, yield: 69%).

HRMS: 523.272509 (found); $C_{26}H_{41}N_3O_6S$, 523.27161 (calcd.). ^1H NMR (600 MHz, $CDCl_3$): 0.82 (1H, d, J = 6.0 Hz), 0.85 (1H, d, J = 6.6 Hz), 1.36 (9H, s), 1.50 (9H, s), 1.74–1.82 (4H, m), 2.05 (1H, m), 2.24 (1H, m), 2.62–2.65 (3H, m), 3.68 (3H, s), 3.86 (1H, d, J = 15.0 Hz), 4.02 (1H, d, J = 10.2 Hz), 4.62 (1H, d, J = 15.6 Hz), 5.53 (1H, s), 10.03 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$): 18.9, 19.4, 22.6, 23.4, 24.0, 28.2, 28.3, 28.6, 29.6, 45.0, 51.8, 52.1, 66.3, 80.3, 126.6, 129.7, 137.5, 153.0, 167.6, 168.8, 170.6.

***N*-(*tert*-butyl)-2-(3-isopropyl-2,5-dioxo-1,2,3,5,6,7,8,9-octahydro-4H-[1]benzothieno [2,3-e][1,4]diazepin-4-yl)acetamide (9a, Method C):** The mixture of **6a** (74.3 mg, 0.25 mmol), valine methyl ester hydrochloride (0.25 mmol, 41.8 mg), triethylamine (0.25 mmol, 34.8 μL), aqueous formaldehyde (0.25 mmol, 18.6 μL), *tert*-butyl isocyanide (0.25 mmol, 28.3 μL) in 0.5 mL of methanol was stirred under RT for 2 days. The reaction was quenched by water and extracted with DCM. The organic layer was washed with saturated potassium carbonate (aq) and dried over anhydrous sodium sulfate. After the evaporation of the solvent, the residue was treated with 0.5 mL of TFA, stirred under 40 °C overnight. To the reaction was added 10 mL of DCM, then neutralized by saturated potassium carbonate (aq). The mixture was extracted with DCM, the organic layer was combined and dried over anhydrous sodium sulfate. After the evaporation of the solvent, the residue was treated with triethylamine (50 μL) and TBD (10 mg) in 0.5 mL of THF, stirred overnight under 40 °C. **9a** was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 2:1) as yellowish solids (22 mg, yield: 23% over three steps). HPLC/MS: t_R = 10.44 min, m/z = 392.3 $[M+H]^+$ HRMS: 391.192778 (found); $C_{20}H_{29}N_3O_3S$, 391.19296 (calcd.). ^1H NMR (600 MHz, $CDCl_3$, major rotamer): 0.92 (1H, d, J = 6.6 Hz), 0.96 (1H, d, J = 6.6 Hz), 1.32 (9H, s), 1.69 (1H, m), 1.77 (1H, m), 1.89–1.96 (3H, m), 2.43 (1H, m), 2.60–2.68 (2H, m), 3.07 (1H, m), 3.70 (1H, d, J = Hz), 4.07–4.16 (2H, ABd, J = Hz), 6.66 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$, major rotamer): 19.4, 20.0, 23.0, 24.5, 25.8, 26.7, 28.6, 51.3, 57.3, 73.8, 122.0, 128.8, 134.7, 140.1, 163.6, 167.6, 170.0.

***N*-(cyclopropylmethyl)-2-(3-isopropyl-2,5-dioxo-1,2,3,5,6,7,8,9-octahydro-4H-[1] benzothieno[2,3-e][1,4]diazepin-4-yl)acetamide (9b, Method C):** The product was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 1:1) as yellowish solids (16 mg, yield: 21% over three steps). HPLC/MS: t_R = 10.10 min; m/z = 490.3 $[M+H]^+$ HRMS: 389.176195 (found); $C_{20}H_{27}N_3O_3S$, 389.17731 (calcd.). ^1H NMR (600 MHz, $CDCl_3$, major rotamer): 0.16–0.19 (2H, m), 0.46- 0.48 (2H, m), 0.88 (3H, d, J = 6.6 Hz), 0.92–0.94 (1H, m), 0.95 (3H, d, J = 6.6 Hz), 1.66–1.76 (2H, m), 1.88–1.96 (3H, m), 2.43–2.46 (1H, m), 2.59–2.66 (2H, m), 3.02–3.08 (2H, m), 3.11–3.14 (1H, m), 3.71 (1H, d, J = 11.4 Hz), 4.17 (1H, ABd, J = 15.0 Hz), 4.25 (1H, ABd, J = 15.0 Hz), 6.91 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$, major rotamer): 3.4, 3.5, 10.6, 19.1, 20.0, 22.3, 23.0, 24.5, 25.9, 26.7, 44.3, 56.1, 73.8, 121.8, 128.6, 134.7, 140.7, 163.7, 168.4, 169.9.

***N*-benzyl-2-(3-isopropyl-2,5-dioxo-1,2,3,5,6,7,8,9-octahydro-4H-[1]benzothieno[2,3-e][1,4]diazepin-4-yl)acetamide (9c, Method C):** The product was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 1:1) as yellowish solids (20 mg, yield: 24% over three steps). HPLC/MS: t_R = 10.50 min; m/z = 426.3 $[M+H]^+$ HRMS: 425.177499 (found); $C_{23}H_{27}N_3O_3S$, 425.17731 (calcd.). ^1H NMR (600 MHz, $CDCl_3$, major rotamer): 0.79 (3H, d, J = 6.6 Hz), 0.90 (3H, d, J = 6.0 Hz), 1.65–1.72 (2H, m), 1.83–1.93 (3H, m), 2.35–2.38 (1H, m), 2.57–2.61 (1H, m), 2.62–2.63 (1H, m), 2.98–3.00 (1H, m), 3.68 (1H, d, J = 11.4 Hz), 4.11 (1H, d, J = 15.0 Hz), 4.33–4.45 (3H, m), 7.22–7.31 (6H, m). ^{13}C NMR (150 MHz, $CDCl_3$, major rotamer): 19.2, 19.9, 22.3, 22.9, 24.5, 25.8, 26.7, 43.5, 56.2, 74.0, 121.7, 127.3, 127.8, 128.6, 128.8, 134.6, 137.9, 140.8, 163.8, 168.5, 169.8.

***N*-(*tert*-butyl)-2-(3-benzyl-2,5-dioxo-1,2,3,5,6,7,8,9-octahydro-4H-[1]benzothieno [2,3-e][1,4]diazepin-4-yl)acetamide (9d, Method A):** The product was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 1:1) as yellowish solids (18 mg, yield: 21% over three steps). HPLC/MS: t_R = 10.89 min; m/z = 440.2 $[M+H]^+$ HRMS: 439.194543 (found); $C_{24}H_{29}N_3O_3S$, 439.19296 (calcd.). ^1H NMR (600 MHz, $CDCl_3$, 1:1 mixture of rotamers): 1.30 (9H, s), 1.34 (9H, s), 1.71–1.81 (4H, m), 1.91–1.95 (4H, m), 2.52–2.66 (6H, m), 2.97 (2H, m), 3.10 (2H, m), 3.20 (1H, m), 3.62 (2H, m), 3.88 (1H, m), 4.09 (1H, m), 4.19 (1H, m), 4.35 (1H, m), 4.49 (1H, m), 5.99 (1H, s), 6.47 (1H, s), 7.05–7.06 (2H, m), 7.21–7.28 (8H, m). ^{13}C NMR (150 MHz, $CDCl_3$, 1:1 mixture of rotamers): 22.3, 22.4, 22.99, 23.03, 24.58, 24.60, 25.5, 26.2, 28.59, 28.63, 32.6, 34.6, 48.3, 51.3, 51.4, 55.4, 57.7, 68.1, 122.3, 122.5, 126.9, 127.3, 128.5, 128.6, 128.9, 129.0, 129.1, 129.45, 129.50, 134.7, 135.0, 135.6, 136.6, 140.2, 141.4, 163.2, 165.5, 167.4, 168.3, 168.4, 169.6.

***N*-(cyclopropylmethyl)-2-(3-benzyl-2,5-dioxo-1,2,3,5,6,7,8,9-octahydro-4H-[1] benzothieno[2,3-e][1,4]diazepin-4-yl)acetamide (9e, Method A):** The product was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 1:1) as yellowish solids (32 mg, yield: 37% over three steps). HPLC/MS: t_R = 10.53 min; m/z = 438.2 $[M+H]^+$ HRMS: 460.1687 (found); $C_{24}H_{27}N_3NaO_3S$, 460.16708 (calcd.). ^1H NMR (600 MHz, $CDCl_3$, 1:1 mixture of rotamers): 0.12 (2H, m), 0.16–0.18 (2H, m), 0.40–0.42 (2H, m), 0.45–0.46 (2H, m), 0.84–0.95 (2H, m), 1.75–1.77 (4H, m), 1.90–1.93 (4H, m), 2.55–2.63 (6H, m), 2.92–2.96 (2H, m), 2.98–3.02 (2H, m), 3.06–3.08 (4H, m), 3.25 (1H, m), 3.56 (1H, m), 3.67–3.75 (2H, m), 4.02 (1H, m), 4.13 (1H, m), 4.22 (1H, m), 4.38 (1H, m), 4.51 (1H, m), 6.44 (1H, m), 6.85 (1H, m), 7.04–7.05 (2H, m), 7.19–7.28 (8H, m). ^{13}C NMR (150 MHz, $CDCl_3$, 1:1 mixture of rotamers): 3.3, 3.4, 10.5, 10.6, 22.3, 22.4, 23.00, 23.04, 24.6, 25.5, 26.2, 32.6, 34.3, 41.0, 44.3, 47.2, 52.1, 54.8, 55.7, 57.8, 68.3, 122.2, 122.3, 126.9, 127.3, 128.57, 128.60, 128.8, 128.9, 129.1, 129.3, 129.4, 129.5, 134.6, 134.8, 135.7, 136.6, 140.7, 141.8, 163.4, 165.7, 168.1, 168.5, 168.8, 169.6.

***N*-(*tert*-butyl)-2-(3-isobutyl-2,5-dioxo-1,2,3,5,6,7,8,9-octahydro-4H-[1]benzothieno [2,3-e][1,4]diazepin-4-yl)acetamide (9f, Method A):** The product was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 1:1) as yellowish solids (11 mg, yield: 14% over three steps). HPLC/MS: t_R = 10.87 min; m/z = 406.2 $[M+H]^+$ HRMS: 405.209380 (found); $C_{21}H_{31}N_3O_3S$, 405.20861 (calcd.). ^1H NMR (600 MHz, $CDCl_3$, a mixture of rotamers): 0.88–0.91 (6H, m), 0.93–0.98 (6H, m), 1.34 (9H, s), 1.37 (5H, s), 1.47–1.50 (2H, m), 1.57–1.65 (3H, m), 1.71–1.75 (3H, m), 1.80–1.82 (2H, m), 1.90–1.93 (4H, m), 2.09 (1H, m), 2.45–

2.54 (2H, m), 2.63–2.71 (3H, m), 2.92 (1H, m), 3.07–3.11 (2H, m), 3.22 (1H, m), 3.32 (1H, m), 3.79 (1H, d, J = 15.6 Hz), 3.94 (1H, d, J = 15.0 Hz), 4.12 (1H, d, J = 15.6 Hz), 4.18 (1H, m), 4.22 (1H, m), 4.31 (1H, d, J = 15.0 Hz), 6.35 (1H, s), 6.46 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$, a mixture of rotamers): 22.0, 22.26, 22.28, 22.32, 22.4, 22.7, 22.8, 22.96, 23.02, 24.55, 24.59, 25.0, 25.1, 25.5, 25.7, 26.0, 28.6, 28.7, 35.0, 37.9, 42.7, 48.3, 50.5, 51.2, 51.3, 51.7, 52.0, 54.8, 56.1, 60.1, 65.1, 122.4, 122.7, 128.7, 129.5, 134.8, 135.0, 139.7, 141.0, 163.5, 165.9, 167.6, 168.2, 168.8, 170.4.

***N*-(*tert*-butyl)-2-[3-(4-hydroxyphenyl)-2,5-dioxo-1,2,3,5,6,7,8,9-octahydro-4H-[1] benzothieno[2,3-e][1,4]diazepin-4-yl]acetamide (9g, Method A):** Sodium bicarbonate was used for the workup instead of saturated potassium carbonate (aq). The product was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 1:1) as yellowish solids (20 mg, yield: 23% over three steps). HPLC/MS: t_R = 9.53 min; m/z = 442.2 $[M+H]^+$ HRMS: 441.173542 (found); $C_{23}H_{27}N_3O_4S$, 441.17223 (calcd.). ^{1}H NMR (600 MHz, CD_3OD): 1.36 (9H, s), 1.50 (1H, m), 1.67–1.77 (3H, m), 2.22 (1H, m), 2.46 (2H, m), 2.70 (1H, m), 2.85 (1H, m), 3.22 (1H, m), 4.13 (1H, m), 4.64 (1H, m), 5.22 (1H, m), 6.62 (2H, m), 6.97 (2H, m), 7.62 (1H, m). ^{13}C NMR (150 MHz, CD_3OD): 22.0, 22.7, 23.7, 25.2, 27.6, 34.1, 43.3, 51.0, 53.3, 63.5, 68.5, 114.8, 123.2, 124.2, 125.2, 128.2, 133.4, 140.3, 156.8, 164.7, 167.7, 170.6.

***N*-(*tert*-butyl)-2-[3-(1H-indol-3-ylmethyl)-2,5-dioxo-1,2,3,5,6,7,8,9-octahydro-4H-[1] benzothieno [2,3-e][1,4]diazepin-4-yl]acetamide (9h, Method A):** The product was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 1:1) as yellowish solids (15 mg, yield: 16% over three steps). HPLC/MS: t_R = 10.68 min; m/z = 479.3 $[M+H]^+$ HRMS: 478.203784 (found); $C_{26}H_{30}N_4O_3S$, 478.20386 (calcd.). ^{1}H NMR (600 MHz, $CDCl_3$, 1:1 mixture of rotamers): 1.32 (9H, s), 1.38 (9H, s), 1.68–1.96 (8H, m), 2.53–2.65 (6H, m), 3.11–3.20 (4H, m), 3.36 (1H, m), 3.68 (1H, m), 3.86 (1H, m), 3.99–4.03 (2H, m), 4.18 (1H, m), 4.48–4.50 (2H, m), 6.01 (1H, s), 6.38 (1H, s), 6.89 (1H, s), 7.05 (1H, s), 7.09–7.13 (3H, m), 7.18 (1H, m), 7.25 (1H, d, J = 7.8 Hz), 7.34 (1H, d, J = 7.8 Hz), 7.53 (1H, d, J = 7.8 Hz), 7.58 (1H, d, J = 7.8 Hz), 8.27 (1H, s), 8.52 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$, 1:1 mixture of rotamers): 22.2, 22.3, 22.4, 23.0, 24.3, 24.5, 24.6, 25.6, 26.3, 28.6, 28.7, 48.0, 51.36, 51.44, 55.6, 56.9, 67.1, 109.3, 110.2, 111.3, 111.4, 118.17, 118.23, 119.6, 122.00, 122.04, 122.1, 122.5, 123.4, 123.8, 126.8, 127.0, 128.8, 129.5, 134.6, 135.1, 135.9, 136.1, 140.0, 141.1, 163.3, 165.7, 167.6, 168.2, 168.7, 170.0.

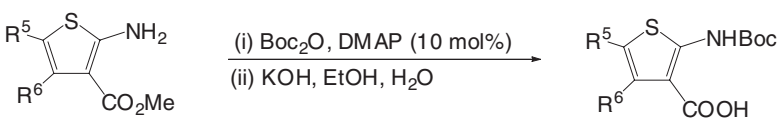
***N*-(*tert*-butyl)-2-(3-isopropyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-thieno[2,3-e][1,4] diazepin-4-yl)acetamide (10a):** The mixture of **6b** (48.6 mg, 0.2 mmol), valine methyl ester hydrochloride (0.2 mmol, 33.5 mg), triethylamine (0.2 mmol, 27.9 μL), aqueous formaldehyde (0.2 mmol, 14.9 μL), *tert*-butyl isocyanide (0.2 mmol, 22.6 μL) in 0.5 mL of methanol was stirred under RT for 2 days. The Ugi product was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 5:1), then treated with 0.5 mL of DCM (10% TFA). The reaction mixture was stirred under RT for 24 h. After the evaporation of the solvent, the residue was treated with triethylamine (100 μL) and TBD (10 mg) in 0.5 mL of THF, stirred overnight under 40 °C. The product was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 1:1) as yellowish solids (5 mg, yield: 7% over three steps). HPLC/MS: t_R = 8.99 min; m/z = 338.3 $[M+H]^+$ HRMS: 337.145879 (found); $C_{16}H_{23}N_3O_3S$, 337.14601 (calcd.). ^{1}H NMR (600 MHz, $CDCl_3$, major rotamer): 0.94 (1H, d, J = 6.6 Hz), 0.98 (1H, d, J = 6.6 Hz), 1.34 (9H, s), 1.95 (1H, m), 3.75 (1H, d, J = 9.6 Hz), 4.03 (1H, d, J = 15.0 Hz), 4.27 (1H, d, J = 15.0 Hz), 6.44 (1H, m), 6.87 (1H, d, J = 6.0 Hz), 8.60 (1H, br.s). ^{13}C NMR (150 MHz, $CDCl_3$, major rotamer): 19.4, 19.9, 27.2, 28.6, 57.2, 73.7, 117.0, 123.8, 128.1, 142.3, 163.2, 167.0, 169.0.

***N*-(*tert*-butyl)-2-(2,5-dioxo-7-phenyl-1,2,3,5-tetrahydro-4H-thieno[2,3-e][1,4] diazepin-4-yl)acetamide (10b):** The mixture of **6c** (63.8 mg, 0.2 mmol), glycine methyl ester hydrochloride (0.2 mmol, 25.0 mg), triethylamine (0.2 mmol, 27.9 μL), aqueous formaldehyde (0.2 mmol, 14.9 μL), *tert*-butyl isocyanide (0.2 mmol, 22.6 μL) in 0.5 mL of methanol was stirred under RT for 2 days. The reaction was quenched by water, and extracted with DCM. The organic layer was washed with saturated potassium carbonate (aq) and dried over anhydrous sodium sulfate. After the evaporation of the solvent, the residue was treated with 1.0 mL of DCM (10% TFA), and stirred under RT for 24 h. After the evaporation of the solvent, the residue was treated with triethylamine (200 μL) and TBD (10 mg) in 0.5 mL of THF, stirred overnight under 40 °C. The product was isolated by silica gel chromatography (petroleum ether/ethyl acetate, 2:1) as yellowish solids (8 mg, yield: 11% over three steps). HPLC/MS: t_R = 9.66 min; m/z = 372.1 $[M+H]^+$ HRMS: 371.128759 (found); $C_{19}H_{21}N_3O_3S$, 371.13036 (calcd.). ^{1}H NMR (600 MHz, CD_3OD): 1.37 (9H, s), 4.09 (2H, s), 4.21 (2H, s), 7.31–7.33 (1H, m), 7.40–7.42 (2H, m), 7.47 (1H, s), 7.58–7.59 (2H, m). ^{13}C NMR (150 MHz, CD_3OD): 27.5, 50.9, 51.1, 52.9, 122.3, 123.3, 124.9, 127.7, 128.8, 133.0, 135.3, 165.0, 167.7, 168.7.

Results and Discussion

Synthesis of 1,4-thienodiazepine-2,5-dione scaffold

As 2-aminothiophenes are optimal starting materials for the synthesis of thienodiazepine backbone, we utilized the versatile Gewald

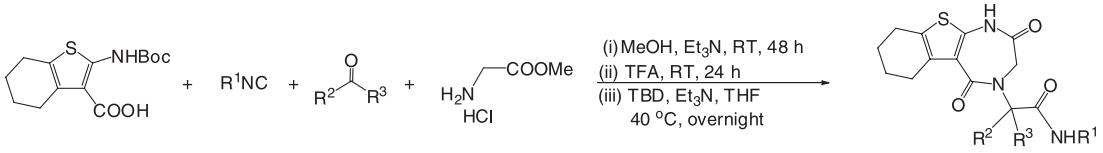


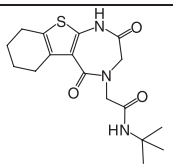
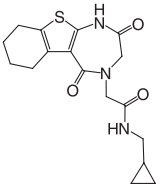
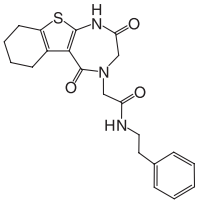
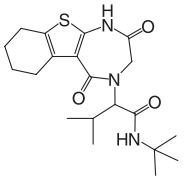
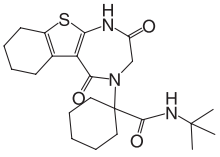
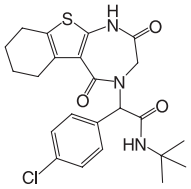
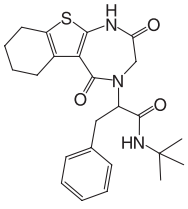
5a, R^5, R^6 = $(-CH_2-)_4$
5b, R^5, R^6 = H
5c, R^5 = Ph, R^6 = H

6a, R^5, R^6 = $(-CH_2-)_4$; 48%
6b, R^5, R^6 = H; 31%
6c, R^5 = Ph, R^6 = H; 47%

Scheme 1: Synthesis of **6a-c**.

Table 1: Ugi-Deprotection-Cyclization approach for the synthesis of 1,4-thienodiazepine-2,5-diones from glycine methyl ester



Entry	R1	Oxo component	Product	Yield (%)
7a	*t*-Bu	Formaldehyde		46[a]
7b	cyclopropyl methyl	Formaldehyde		17[a]
7c	phenyl ethyl	Formaldehyde		13[a]
7d	*t*-Bu	Isobutylaldehyde		15[a]
7e	*t*-Bu	Cyclohexanone		10[a]
7f	*t*-Bu	*o*-chloro-benzaldehyde		37[b]
7g	*t*-Bu	Benzylaldehyde		21

[a]Method A, isolated yields (over three steps).
[b]Method B, isolated yields (over two steps).

MCRs to prepare compounds **5a-c**. We recently developed a general synthetic protocol to synthesize Boc protected thiophene carboxylic acids **6a-c** (Scheme 1) (32). In the first step, 2-aminothiophenes **5a-c** were obtained by the Gewald reaction of cyclohexanone, 1,4-dithiane-2,5-diol, and phenylacetaldehyde, respectively. In the second step, *N*-Boc thiophene carboxylic acids **6** were prepared by Boc protection of **5** and following hydrolysis transformation. Hence, we intended to employ the bifunctional orthogonally protected intermediates **6** and amino acid-derived methyl esters for the synthesis of new TDZ scaffold via UDC approach.

The synthetic method was designed to allow rapid access to TDZs in just three steps from the variable precursor building blocks. Initially, we tried the Ugi reaction of **6a**, *tert*-butyl isocyanide, formaldehyde, with glycine methyl ester hydrochloride in the presence of triethylamine under room temperature for 48 h. After simple extraction workup, the intermediate Ugi product was subjected to deprotection with TFA and subsequent cyclization using a catalytic amount of TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene). The product **7a** was isolated by chromatography in 46% yield over three steps. The 'three-step, one-separation' procedure was applied for the synthesis of **7a-e** with variable isocyanides and oxo components (Table 1). Interestingly, compounds **7f** and **7g** were obtained in two steps after the treatment with TFA. It's possible that the intramolecular cyclization is favorable even without the treatment of TBD (29).

Next, we investigated a series of amino acid methyl esters for the synthesis of new TDZ scaffolds. We tried the Ugi reaction of **6a**, *tert*-butyl isocyanide, formaldehyde with valine methyl ester hydrochloride in the presence of triethylamine under room temperature for 24 h (Scheme 2). The Ugi product **8** was isolated by chromatography in 69% yield. The deprotection of **8** and the following cyclization afford **9a** in 59% yield over two steps (41% over three steps). Running the sequence without any isolation yielded compound **9a** 23%. Although the overall yield is lower, the 'three-step, one-separation' procedure avoids the additional separation step.

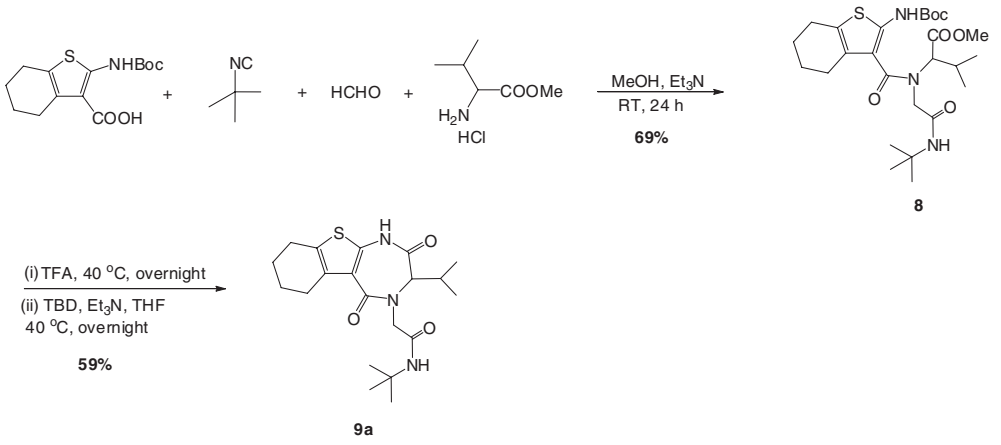
Hence, **6a** was applied to UDC approach for the synthesis of TDZs with variable amino acid derivatives (Table 2). Valine, phenylalanine, leucine, 4-hydroxy phenylglycine, tryptophan methyl esters as well as several isocyanides are tolerant to this procedure. Compounds **9a–h** were isolated by chromatography in 14–37% yield over three steps. As TBD serves as the catalyst, racemization of chiral center at amino acid nucleus is unclear (33).

We also investigated other aminothiophene backbones **6b** and **6c** for the synthesis of TDZs (Table 3). The corresponding Ugi product of **6b** was isolated by chromatography in 46% yield. Compound **10a** was obtained in 16% yield by the further transformation of the Ugi product. A 10% solution of TFA in dichloromethane was used for the deprotection step under a mild condition. Similarly, compound **10b** was isolated by chromatography in 11% yield over three steps.

Conformation analysis of TDZ scaffold

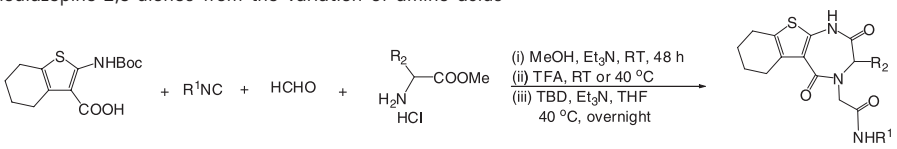
NMR spectra of some compounds substituted with amino acid side chains show clearly the presence of two rotamers, which are not chromatographically separable. For instance, compounds **9d**, **9e**, and **9h** show two rotamers at a ratio of 1:1 in $CDCl_3$. The population of rotamers was found related to the deuterium solvent used. For example, the ratio of **9d** shows roughly 2:3 in CD_3OD (Figure S1 in Supporting Information). This observation suggests that seven-membered diazepine nucleus of thienodiazepinedione is quite rigid, similar to the scaffold of benzodiazepinediones (34,35). The energy barrier for the interconversion of benzodiazepinedione conformers (pseudo-axial and pseudo-equatorial conformers) was calculated up to 14.8 kcal/mol (11). We also speculate that 1,4-thienodiazepine ring inversion is slow enough, therefore conformers can be detected by NMR under room temperature.

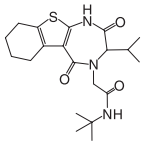
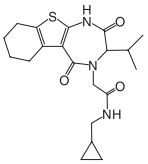
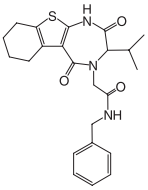
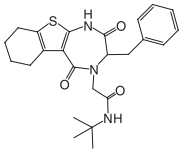
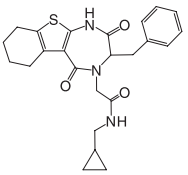
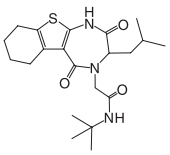
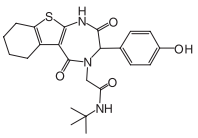
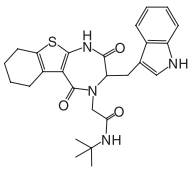
Recently, we used MCR methods to develop α-helix mimetics, which could become very important lead structures to (ant-)agonize protein–protein interactions (36). In our ongoing interest for the application of peptidomimetic structures generated from MCRs, the design and synthesis of peptide β-turn mimetic scaffolds and libraries are also desirable (37). A β-turn is most often defined as any tetrapeptide unit occurring in a non-helical region that causes a reversal of the direction of the peptide chain



Scheme 2: Synthesis of **9a**.

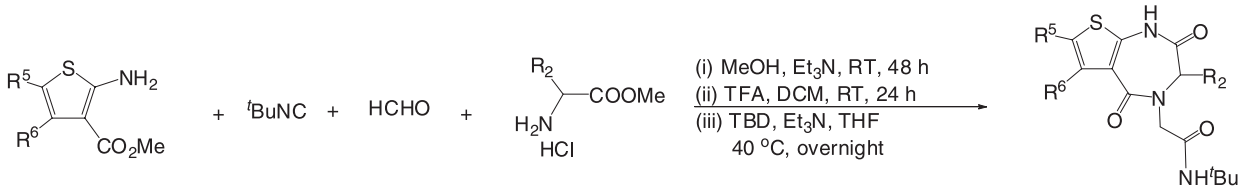
Table 2: 1,4-Thienodiazepine-2,5-diones from the variation of amino acids

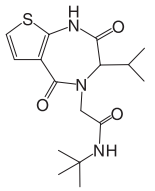
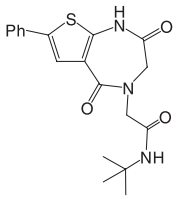


Entry	R^1	Amino acid	Product	Yield (%)
9a	*t*-Bu	Valine		23[b]
9b	cyclopropyl methyl	Valine		21[b]
9c	benzyl	Valine		24[b]
9d	*t*-Bu	Phenylalanine		21[a]
9e	cyclopropyl methyl	Phenylalanine		37[a]
9f	*t*-Bu	Leucine		14[a]
9g	*t*-Bu	4-hydroxy phenylglycine		23[a]
9h	*t*-Bu	Trptophan		16[a]

[a]Method A, isolated yields (over three steps).
[b]Method C, isolated yields (over three steps).

Table 3: 1,4-Thienodiazepine-2,5-diones from the variation of aminothiophenes



Entry	R^5	R^6	Amino acid	Product	Yield[a] (%)
10a	H	H	Valine		7
10b	Ph	H	Glycine		11

[a]isolated yields, over three steps.

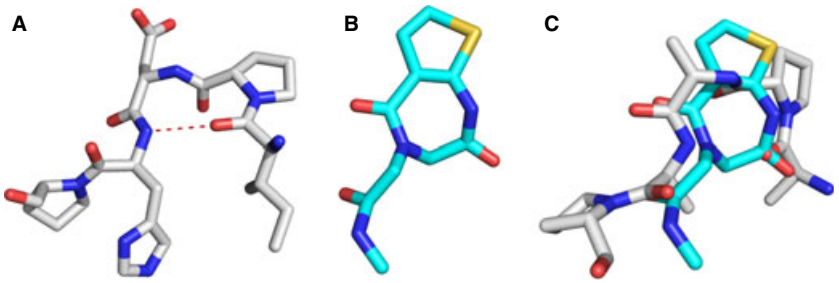


Figure 4: (A) Structure of a typical β-turn. The PDB code for the protein is 1H2C (chain A, turn region Ile142-Pro146). (B) The core scaffold was chosen as a model of the investigated β-turn mimetic. (C) Minimized conformation of core scaffold as a β-turn mimetic superimposed onto a type II β-turn. For clarity, only the backbone and α atoms are shown.

(Figure 4A) (38). As 1,4-benzodiazepines were found to act as β-turn mimetics (7–9), we speculate that our TDZ scaffold could also have β-turn mimetic moiety. Thus, the tripeptide fragment of TDZ scaffold was compared with known protein β-turns (Figure 4). The core scaffold was investigated as a model superimposed onto a type II β-turn backbone (PDB code: 1H2C, turn region Ile142-Pro146).

Cheminformatics study of TDZ scaffold

Owing to in silico and computational advances, chemoinformatics would help to identify promising scaffolds of greater importance in lead discovery (39). We generated a virtual compound library (N = 50 000) from a random sample of starting materials to evaluate the chemical space of the TDZs (Supplemental Information). These compounds generated from the virtual library were introduced into Instant JChem (Instant JChem 2.5.1, 2009, www.chemaxon.com) for calculating their physical properties. The distributions of this random virtual library (N = 50 000) and commercial available benzodiazepines (N = 2498) were presented in Figure 5. This new scaffold covers unexplored chemical space of benzodiazepine family. Owing to the diversity of chemical space, this scaffold is potentially useful for virtual screening and lead discovery.

To evaluate the potential of combinatorial library design, the physicochemical properties of the virtual compound library (N = 50 000) were calculated (40). The data were analyzed statistically by frequency distributions in PASW Statistics 18 (Figure S2 in Supplemental Information). Because of the diversity of reactant components, the range of molecular weight is between 267.3 Da. and 580.7 Da.

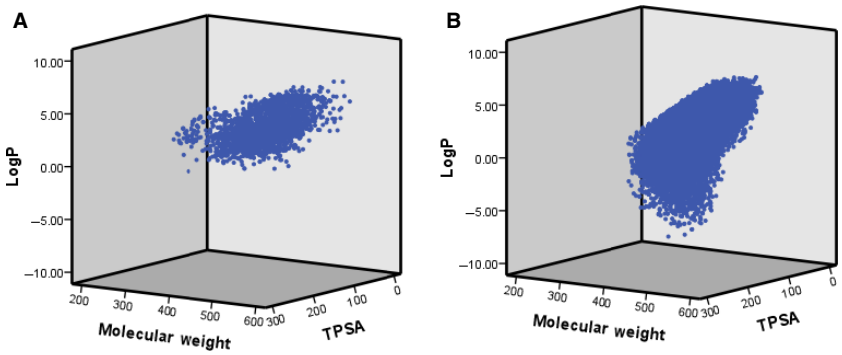


Figure 5: Comparison of chemical space distribution: (A) benzodiazepine library of a substructure search from eMolecules (N = 2498); (B) a random virtual library of 1,4-thienodiazepine-2,5-diones (N = 50 000).

Table 4: Physicochemical properties of synthesized compounds (N = 17) and a random virtual library (N = 50 000)[a]

Mean	MW (Da)	LogP	Total polar surface area (Å^2)	Number of rotatable bonds	Hydrogen bond acceptors	Hydrogen bond donors
Synthesized compounds	407.1 ± 40.7	3.73 ± 0.94	108.9 ± 6.0	4 ± 1	4 ± 0	2 ± 0
Virtual library	453.7 ± 44.1	2.46 ± 1.84	149.6 ± 27.3	7 ± 2	6 ± 1	3 ± 1

[a]All values listed are mean value ± standard deviation.

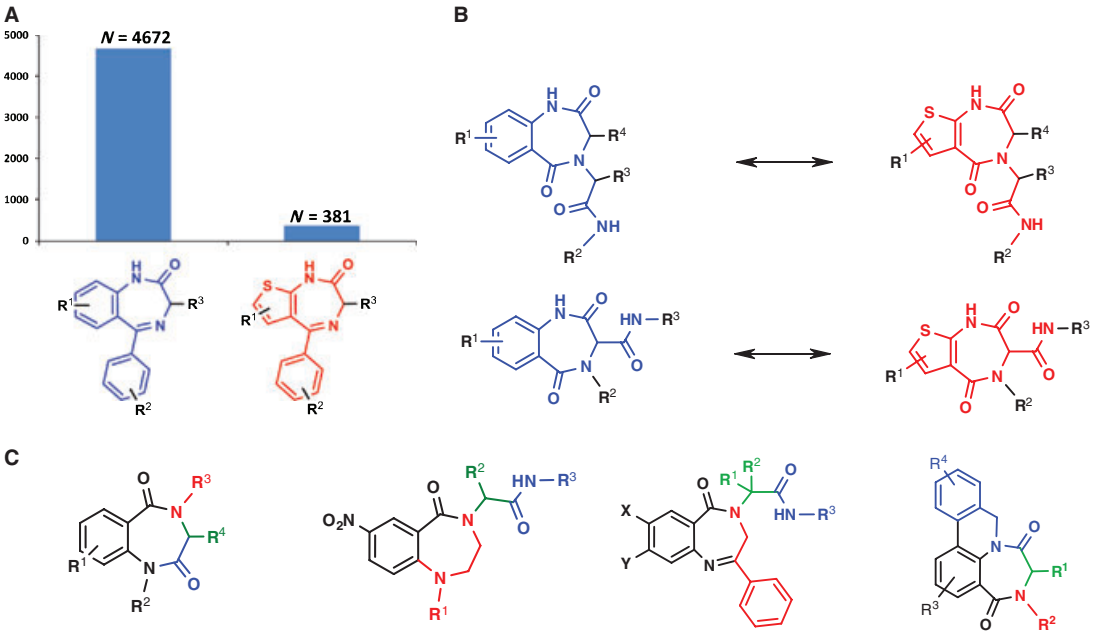


Figure 6: (A) Known structures; (B) multicomponent reaction (MCR) accessible isosteric azepine scaffolds; (C) Other MCR accessible benzodiazepines. The scaffold space of benzodiazepines accessible by MCR is very rich. Six different scaffolds can be synthesized using different isocyanide-based MCR strategies. Of the bioisosteric thienodiazepines currently only two scaffolds are generally amenable by MCR. Armstrong et al. (28,42), Hulme et al. (43), Tempest et al. (44), Marcaccini et al. (45) and Zhu et al. (46).

The mean of LogP is 2.46 with standard deviation of 1.84, which indicates acceptable permeability of most compounds. Total polar surface area of the majority of compounds is between 122.3 Å^2 and 176.9 Å^2. The mean number of rotatable bonds (NRB), hydrogen bond acceptors (HBA), and hydrogen bond donors (HBD) are shown in Table 4. In terms of drug likeness, 79.7% of 50 000 compounds obey Lipinski's rule. And 93.7% of them are predicted to be bioavailable (mass ≤ 500, LogP ≤ 5, HBD ≤ 5, HBA ≤ 10, polar surface

area ≤ 200, NRB ≤ 10, fused aromatic rings ≤ 5). For comparison, the physicochemical properties of synthesized compounds (N = 17) and a random virtual library (N = 50 000) were summarized in Table 4. The structure-property relationship indicates the rationale of diversity-oriented library design with drug-like properties. Moreover, 3D structures of a random virtual library were generated by the software Omega (Supplemental Information). The compound library of this new thienodiazepine scaffold (N = 5000) could be used for docking program and other virtual analysis software to discover possible hits of suitable receptors.

Scaffold Hopping

Isofunctional molecules based on different chemical scaffolds are key to the early drug development process. Leads based on different scaffolds can be found by a process called scaffold hopping (41). This process can rely on known or intuitive bioisosteres or on advanced chemoinformatic strategies. Early development of several leads based on different scaffolds has the advantage of reducing the very high attrition rate in preclinical and early clinical development. Additionally, scaffold hopping has great implications for the maintenance of intellectual property. For example, for the benzodiazepine scaffold 4672 structures are registered in SciFinder, whereas only 381 thienodiazepines are known (Figure 6A). We described here two thienodiazepine scaffolds with different 2D and 3D distribution of HBD and acceptors. They are clearly related to their benzodiazepine scaffolds amenable by the UDC method (Figure 6B,C). The chemical space behind the four related scaffolds is, however, very much different, as the thiophene building block allows for many more simple variations based on the versatile Gewald MCR.

Conclusions and Future Directions

In summary, we have synthesized a series of TDZs by using the union of Gewald reaction and UDC strategy. This approach possesses novel hybrid peptidomimetic 1,4-diazepines with well-defined diversity, which can be achieved from readily available starting materials. UDC strategy allows convenient preparation of TDZs without using the traditional peptide coupling methods. Similar to the compound libraries of benzodiazepines, the TDZ scaffold could also be suitable for high-dimensional combinatorial synthesis to meet the screening purpose. The conformation analysis and chemical space of this novel scaffold was studied. Based on the commonly accepted descriptors, it is potentially useful to obtain lead-like compounds based on this scaffold.

Acknowledgment

This work was supported by the NIH grant 1R21GM087617-01 (to AD) and is part of a NCI-RAND program.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Appendix S1. Supplemental information.

Figure S1. NMR spectra of compound **9d** in $CDCl_3$ and CD_3OD.

Figure S2. Statistical distributions of physical properties of a random virtual library (N = 50 000).

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